

REMARKS

Claims 2, 4, 6, 12, 16, 19-56 are pending. Claims 2, 4, 6, 19, 29, 32, 33, and 34 have been amended without prejudice and without acquiescence. Claims 41-56 have been added. Support for the amendments and new claims can be found throughout the specification and claims, for example, page 2, lines 23-30, page 3, 8-29, page 6, lines 1-3, page 8, lines 31-34, page 9, lines 1-5, and page 13, lines 1-23. No new matter has been added.

The issues outstanding in this application are as follows:

- Claims 2, 20 and 21 were rejected under 35 U.S.C. § 102(b) as being anticipated by Ronaghi et al. (Anal. Biochemistry, 1996).
- Claims 2, 4, 6, 12, 16 and 19-31 and 33, 34, and 37-40 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Ronaghi et al., in view of Mian et al., (US 6,319,469).
- Claims 2, 4, 6, 12, 16 and 19-40 were rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification.

Applicants respectfully traverse the outstanding rejections, and Applicants respectfully request reconsideration and withdrawal thereof in light of the amendments and remarks contained herein.

I. 35 U.S.C. § 102(b)

Claims 2, 20 and 21 are rejected under 35 U.S.C. § 102(b) as being anticipated by Ronaghi et al. (Anal. Biochemistry, 1996). The Action states that Ronaghi et al. teaches the methods of using a microfluidic device to determine a nucleotide base in a nucleic acid sample. Applicants respectfully traverse.

The teachings employed by Ronaghi et al. do not anticipate the claims found in the present application. Applicants remind the Examiner that “[u]nder 35 U.S.C. § 102, anticipation requires that...the prior art reference must be enabling, thus placing the allegedly disclosed matter in the possession of the public.” See *Akzo N.V. v. United States Int’l Trade Comm’n*, 808 F.2d 1471, 1 USPQ2d 1241, 1245 (Fed. Cir. 1986) (citing *In re Brown*, 329 F.2d 1006, 1011, 141 USPQ 245, 249 (C.C.P.A. 1964).

Applicants assert that the phrase on page 88 of Ronaghi et al., which states “a flow system, with small volumes, high speed and low cost”, has been erroneously construed by the Examiner. This phrase may suggest some sort of flow device, however, it does not teach or suggest forming immobilized DNA in one or more reaction areas in a microchannel of a microfluidic device, and sequentially adding reagents to the microchannel, moving the reagents to the reaction areas, detecting if addition to the primer has occurred, removing reagents, and then repeating the steps with another deoxynucleotide/deoxynucleotide analogue. Ronaghi et al. merely mentions a “flow system”; it does not teach how to perform Ronaghi’s method in any type of flow system. Yet further, there is no indication that the flow system as stated in Ronaghi et al. would move reagents to a reaction area in a microchannel structure of a microfluidic device as stated in the present specification. The mere mention of the phrase “flow system” in Ronaghi does not provide any guidance for one of skill in the art to perform the method of independent claim 2.

Yet further, the Examiner continues to state that Ronaghi et al teaches that DNA can be immobilized to a capillary. Ronaghi may state the possibility of immobilizing DNA to a capillary, however, Ronaghi et al does not teach how this capillary would constitute a part of a microchannel structure of a microfluidic device in which the microchannel structure comprises one or more reaction areas or reaction chambers. Nor does it teach if and/or how

reagents are moved in the capillary. Thus, the mere mention of immobilizing DNA to a capillary does not teach all the limitations of independent claim 2.

Applicants remind the Examiner that inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient to establish inherency. *See Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). Inherent anticipation requires that the missing descriptive material is "necessarily present," not merely probably or possibly present, in the prior art. *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). Inherency does not embrace probabilities or possibilities. *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1951 (Fed. Cir. 1999). In view of this case law, Applicants contend that Rongahi may use the words "flow system" and "capillary", however, Rongahi et al does not literally or inherently teach all the steps that are involved in independent claim 2.

Thus, Applicants assert Rongahi et al does not meet all the requirements to establish a *prima facie* case of anticipation and therefore, request that the rejection be withdrawn.

II. 35 U.S.C. § 103(a)

Claims 2, 4, 6, 12, 16 and 19-31 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ronaghi et al. in view of Mian et al., (US 6,319,469). The Action states that Ronaghi et al. teaches a method of identifying a sequence of a portion of DNA, but does not teach identifying a sequence of a portion of DNA using a microfluidic device. The Action further states that Mian et al. teaches the use of a microfluidic device for the method of Ronaghi et al. Applicants respectfully traverse.

Applicants respectfully remind the Examiner that section 103 requires consideration of the claimed invention "as a whole." This "as a whole" requirement prevents evaluation of the invention part by part, in hindsight. *Env'tl. Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 698 (Fed. Cir. 1983). Without this requirement, an obviousness assessment could break an invention into its component parts (e.g., a microfluidic device and a sequencing method), then find a prior art reference containing the component parts (e.g., a microfluidic device as described by Mian and sequencing method as described by Rongahi), and on that basis alone declare the invention obvious. The courts have refused to act on this type of hindsight

reasoning, which uses the invention as a roadmap to find its prior art components. This type of analysis discounts the value of novel selection inventions. Thus, the courts have required that an Examiner must show some suggestion or motivation, excluding the invention itself, to make the new combination. See *In re Rouffet*, 149 F.3d 1350, 1355-56 (Fed. Cir. 1998); *In re Lee* 277 F. 2d 1338, 61 USPQ 2d 1430 (Fed. Cir. 2002); and c.f. *Ruiz v. A.B. Chance Co.*, F.3d 1270 (Fed. Cir. 2004).

Firstly, on page 11 of the Action, the Examiner has erroneously summarized a vital section of the previous response filed on January 20, 2004. On page 10 (2¶ and 3¶) of Applicants' January 20, 2004 response, Applicants argued that Mian **does** teach sequencing using labeled didoxynucleotide (Example 7, column 48-column 49). In fact, the importance of the argument in the January 20, 2004 response was to illustrate that the sequencing method of Mian uses labeled didoxynucleotide, which is opposite of the sequencing method described by Ronaghi, which does not use labeled dideoxynucleotides. On page of 11 of the Action, the Examiner states that Applicants argued that Mian **does not** teach the use of labeled dideoxynucleotides. In view of this statement by the Examiner, Applicants assert that the Examiner has misstated Applicants previous remarks filed in January 20, 2004 and request that this be corrected.

As the Applicants have previously argued, the sequencing method of Ronaghi et al. requires a stepwise addition of nucleotides and extension of primer is measured. Thus, only one of the four nucleotides is added at any give time. The DNA sequencing taught by Mian et al. is enzymatic sequencing by the Sanger method. The Sanger method requires extending the primer in the presence of all four nucleotides and trace amounts of a fluorescently labeled dideoxynucleotide. Thus, all four nucleotides are added simultaneously to a single reaction mixture, not individually as taught in Ronaghi et al. Yet further, in the Sanger method as used by Mian et al., once the reaction has occurred, **electrophoresis is required** to separate the dideoxynucleotide-terminated DNA fragments so that the sequence can be determined by the fluorescent pattern of the DNA fragments. In Ronaghi et al., **electrophoresis is not required** after each reaction. Thus, Applicants assert that the sequencing methods of Mian et al. and Ronaghi et al. are not similar and one of skill in the art would not combine the references.

On page 9 of the Action, the Examiner states that claims 6, 22, 25, 26, and 29-31 indicate the limitation of a fluorescently labeled dideoxynucleotide. Claims 2, 4, and 19, as well as, dependent claims 6, 25, and 29, were amended without prejudice and without acquiescence to remove the term dideoxynucleotide. These amendments have been made in order to overcome a rejection under 35 U.S.C. 112 1st paragraph (alleged lack of support for removal of dideoxynucleotide in washing/removing step), but will also make this rejection under 35 U.S.C. § 103(a) moot.

The Examiner further states that Mian et al. in col 34, line 40 teaches that “real time control capabilities are also provided”. Applicants assert that the Examiner has misconstrued this phrase. This phrase refers to a system, such as a computer system, having various software applications to perform the analysis, etc. Applicants assert that this phrase in Mian et al. does not provide a suggestion to perform real time DNA sequencing as contemplated in the present specification, i.e. continuously monitoring the sequencing reactions (base incorporation) in real time (see p. 10, lines 14-19 of our specification). This is not possible with the DNA sequencing method described in Mian.

In view of the above arguments and amendments, Applicants assert that the Examiner is using impermissible “hindsight” to express motivation to combine the references of Ronaghi et al. and Mian et al. *See In re McLaughlin* 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971).

Thus, with the lack of teaching or suggestion to design a microfluidic device that is capable of immobilizing DNA molecules, moving liquids and performing cycles of sequencing reactions in which each cycle is represented by a separate step comprising addition of deoxynucleotide, or deoxynucleotide analogue to a nucleic acid molecule (DNA primer), Applicants assert that the references do not meet the basic requirements of a *prima facie* case of obviousness. Accordingly, Applicants respectfully submit reconsideration and withdrawal of the outstanding rejection under 35 U.S.C. 103(a) as being unpatentable over Ronaghi et al. in view of Mian et al.

III. 35 U.S.C. § 112, first paragraph rejection

Claims 2, 4, 6, 12, 16, and 19-31 are rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described. The Examiner states that the limitation

of “removing pyrophosphate, DNA polymerase or dideoxynucleotide” in claims 2, 4, and 19 appears to be new matter. Applicants respectfully traverse.

The fundamental inquiry is whether the material added by amendment was inherently contained in the original application. *Vas Cath Inc. v. Mahurkar*, 932 F.2d 1555,1563, 19 USPQ2d 111, 1116 (Fed. Cir. 1991).

The Examiner also states that basis was found on page 2 and page 8 for the inclusion of a step that removes or washes away excess deoxynucleotide or deoxynucleotide analogue. Thus, in order to advance the prosecution of this application, Applicants have amended without prejudice and without acquiescence independent claims 2, 4, and 19 to indicate that deoxynucleotide or deoxynucleotide analogue are removed, which the Examiner has clearly indicated Applicants describe. Thus, in light of these amendments, this rejection is now moot and, Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 06-2375, under Order No. 10104789 from which the undersigned is authorized to draw.

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Respectfully submitted,

By 

Melissa W. Acosta

Registration No.: 45,872

FULBRIGHT & JAWORSKI L.L.P.

1301 McKinney, Suite 5100

Houston, Texas 77010-3095

(713) 651-5407

(713) 651-5246 (Fax)